CLAIMS

1. A bioreductive conjugate comprising a non-cytotoxic bioreductive moiety with linked thereto at least one therapeutic agent, and salts thereof, said conjugate being such that on bioreduction the therapeutic agent is released with generation of a species having an alkylating centre and being capable of undergoing a self-alkylation reaction to generate a non-cytotoxic residue of the bioreductive moiety.

2. A bioreductive conjugate as claimed in claim 1 of formula I:

$$A\,(B)_n \qquad (I)$$

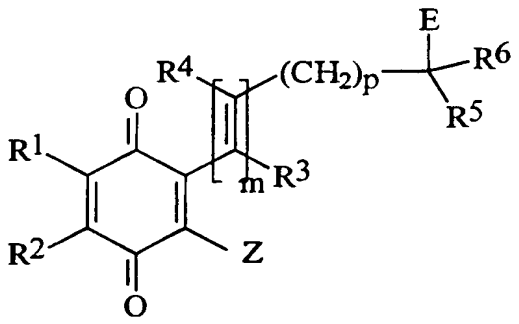
(where A is a non-cytotoxic bioreductive moiety, each B is independently the residue of a therapeutic agent, and n is an integer) or a salt thereof.

3. A bioreductive conjugate as claimed in claim 2, wherein in formula I, n is 1 to 3.

4. A bioreductive conjugate as claimed in claim 2 or claim 3, wherein A and B are stably conjugated in an oxygenated environment and are such that following reductive activation of A, A and B detach and either A is itself a stable, non-cytotoxic species, or A reacts with itself to form a stable, non-cytotoxic species.

5. A bioreductive conjugate as claimed in any one of claims 1 to 4, wherein said bioreductive moiety is substantially non-mutagenic.

6. A bioreductive conjugate as claimed in claim 1 of the formula II:



(II)

(wherein

R^1 and R^2 independently represent hydrogen or halogen atoms, or a group R, OR, SR, NHR, NR_2, CO_2R or CONHR;

or, alternatively, R^1 and R^2 together with the intervening ring carbon atoms form a 5-7 membered carbocyclic or heterocyclic ring itself optionally substituted by one or more halogen atoms, or by one or more groups selected from R, OR, SR, NHR, NR_2, CO_2R and CONHR;

Z represents an alkyl, alkenyl, aryl or aralkyl group optionally carrying at least one OH, SH, NH_2 or NHR^7 group in which R^7 is an alkyl group;

R^3, R^4, R^5 and R^6 independently represent hydrogen atoms or an alkyl or alkenyl group;

each group R independently represents a hydrogen atom, an alkyl or alkenyl group;

E represents the residue of a therapeutic agent to be delivered, optionally attached via a linking group L;

m = 0, 1, 2 or 3; and

p = 0 or 2;

with the proviso that when m = 1 then p = 0)

or a salt thereof.

7. A bioreductive conjugate as claimed in claim 6, wherein in formula II:

Z represents a group of the formula $(CH_2)_nXH$;

n = 0, 1, 2 or 3;

X represents an oxygen or sulphur atom, or a group of formula NY in which Y represents a hydrogen atom or an alkyl group;

or a salt thereof.

8. A bioreductive conjugate as claimed in claim 6, wherein in formula II:

Z represents a group of the formula $(CH_2)_nXH$ in which X represents an amino group;

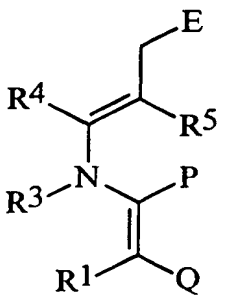
R^1 and R^2 each represent alkoxy groups or, together with the intervening ring carbon atoms, R^1 and R^2 form a benzene ring;

R^3, R^4, R^5 and R^6 each represent hydrogen atoms; and

n = 0, m = 1 and p = 0;

or a salt thereof.

9. A bioreductive conjugate as claimed in claim 1 of formula III:



(III)

(wherein

P and Q together with the intervening ring carbon atoms form a quinone or indoloquinone ring, a nitroaromatic, N-oxide or diazoaromatic compound, itself optionally substituted by one or more halogen atoms, or by one or more groups selected from R, OR, SR, NHR, NR_2, CO_2R and CONHR;

R^1 represents a hydrogen or halogen atom, or a group R, OR, SR, NHR, NR_2, CO_2R or CONHR;

R^3, R^4 and R^5 independently represent hydrogen atoms or an alkyl or alkenyl group;

each group R independently represents a hydrogen atom, an alkyl or alkenyl group; and

E represents the residue of a therapeutic agent to be delivered, optionally attached via a linking group L)

or a salt thereof.

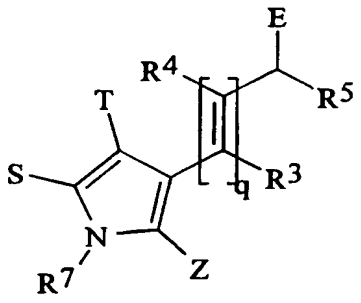
10. A bioreductive conjugate as claimed in claim 9, wherein in formula III:

P and Q together with the intervening ring carbon atoms form a quinone or indoloquinone ring; and

R^1, R^3, R^4 and R^5 each represent hydrogen atoms or methyl groups;

or a salt thereof.

11. A bioreductive conjugate as claimed in claim 1 of formula IV:



(IV)

(wherein

S and T together with the intervening ring carbon atoms form a quinone or iminoquinone ring, a nitroaromatic or N-oxide compound, itself optionally substituted by one or more halogen atoms, or by one or more groups selected from R, OR, SR, NHR, NR_2, CO_2R and CONHR;

Z represents an alkyl, alkenyl, aryl or aralkyl group optionally carrying at least one OH, SH, NH_2 or NHR^6 group in which R^6 is an alkyl group;

R^7 represents an alkyl group;

R^3, R^4 and R^5 independently represent hydrogen atoms or an alkyl or alkenyl group;

each group R independently represents a hydrogen atom, an alkyl or alkenyl group;

q = 0, 1, 2 or 3; and

E represents the residue of a therapeutic agent to be delivered, optionally attached via a linking group L)

or a salt thereof.

12. A bioreductive conjugate as claimed in claim 11, wherein in formula IV:

S and T together with the intervening ring carbon atoms form a quinone or N-oxide compound;

R^3, R^4 and R^5 each represent hydrogen atoms;

R^7 is methyl;

Z represents a group of formula $(CH_2)_nXH$ wherein X represents an oxygen or sulphur atom, or X represents a group of formula NY in which Y represents a hydrogen atom or an alkyl group; and

q = 0 or 1,

or a salt thereof.

13. A bioreductive conjugate as claimed in any one of claims 1 to 5, wherein said bioreductive moiety comprises a quinone, naphthoquinone, indoloquinone, quinolino quinone or a derivative thereof.

14. A bioreductive conjugate as claimed in claim 13, wherein said bioreductive moiety is a 1,4-benzoquinone, a naphthoquinone, or a derivative thereof, in which the quinone ring carries an optionally hydroxy- or amino-substituted alkenyl group and an adjacent nucleophilic moiety.

15. A bioreductive conjugate as claimed in any one of claims 1 to 5, wherein said bioreductive moiety is a

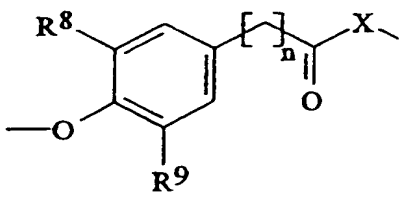
1,4-benzoquinone and the therapeutic agent is dexamethasone.

16. A bioreductive conjugate as claimed in any preceding claim, wherein said bioreductive moiety is linked to said therapeutic agent via a linker group L comprising an ester, phosphate ester, ether, amine, thiol or thiol ester group or any combination thereof.

17. A bioreductive conjugate as claimed in claim 15 wherein said linker group L is a group of the formula:

$$-O-CO-(CH_2)_n-CO-X-$$

or



(wherein n is an integer from 1 to 3;

X represents a sulphur or oxygen atom; and

R^8 and R^9 each independently represent F or Cl).

18. A bioreductive conjugate comprising a non-cytotoxic bioreductive noiety with linked thereto at least one therapeutic agent, and salts thereof, said conjugate being such that on bioreduction the therapeutic agent is released with generation of a species having a sterically hindered alkylating centre to prevent alkylation of biomolecules.

19. A process for the preparation of a bioreductive conjugate as claimed in any of claims 1 to 18, said process comprising linking at least one therapeutic agent to a non-cytotoxic bioreductive moiety.

20. A pharmaceutical composition comprising a bioreductive conjugate as claimed in any one of claims to 18, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutical carrier or excipient.

21. A bioreductive conjugate as claimed in any one of claims 1 to 18 for use in a method of targeting a therapeutic agent to a site of hypoxia and/or ischemia within the human or non-human animal body.

22. A bioreductive conjugate as claimed in any one of claims 1 to 18 for use in treatment of rheumatoid arthritis or other arthritic conditions, diabetes, atherosclerosis, stroke, sepsis, Alzheimer's disease and other neurological disorders, cancer, kidney disease, digestive diseases, liver disease, chronic periodontitis or ischemia following tissue transplantation.

23. Use of a bioreductive conjugate as claimed in any one of claims 1 to 18 in the manufacture of a medicament for use as a targeting agent capable of targeting a site of hypoxia and/or ischemia within the human or non-human animal body.

24. Use as claimed in claim 22 for the treatment of rheumatoid arthritis or other arthritic conditions, diabetes, atherosclerosis, stroke, sepsis, alzheimer's disease and

other neurological disorders, cancer, kidney disease, digestive diseases, liver disease, chronic periodontitis or ischemia following tissue transplantation.

25. A method of targeting hypoxic and/or ischemic tissues in the human or non-human animal body, said method comprising administering to said body a bioreductive conjugate as claimed in any one of claims 1 to 18.